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Items 1 - 19 of 19

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[My NCBI](#)☐ 2: [Seki T, Wang MH, Miyata N, Laniado-Schwartzman M.](#)[Related Articles, Links](#)☒ Cytochrome P450 4A isoform inhibitory profile of N-hydroxy-N'-(4-butyl-2-methylphenyl)-formamidine (HET0016), a selective inhibitor of 20-HETE synthesis. Biol Pharm Bull. 2005 Sep;28(9):1651-4. PMID: 16141533 [PubMed - indexed for MEDLINE]☐ 3: [Guo M, Roman RJ, Falck JR, Edwards PA, Scicli AG.](#)[Related Articles, Links](#)☒ Human U251 glioma cell proliferation is suppressed by HET0016 [N-hydroxy-N'-(4-butyl-2-methylphenyl)formamidine], a selective inhibitor of CYP4A. J Pharmacol Exp Ther. 2005 Nov;315(2):526-33. Epub 2005 Aug 4. PMID: 16081682 [PubMed - indexed for MEDLINE]☐ 4: [Parmentier JH, Lavrentyev EN, Falck JR, Capdevila JH, Malik KU.](#)[Related Articles, Links](#)☒ Evaluation of cytochrome P450 4 family as mediator of phospholipase D activation in aortic vascular smooth muscle cells. Life Sci. 2005 Jul 15;77(9):1015-29. PMID: 15964316 [PubMed - indexed for MEDLINE]☐ 5: [Benter IF, Yousif MH, Canatan H, Akhtar S.](#) [Related Articles, Links](#)[Related](#)  
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-  Inhibition of Ca<sup>2+</sup>/calmodulin-dependent protein kinase II, RAS-GTPase and 20-hydroxyeicosatetraenoic acid attenuates the development of diabetes-induced vascular dysfunction in the rat carotid artery.  
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J Appl Physiol. 2005 Mar;98(3):772-9. Epub 2004 Nov 5.  
PMID: 15531567 [PubMed - indexed for MEDLINE]
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Circ Res. 2004 Feb 6;94(2):167-74. Epub 2003 Dec 11.  
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- ☐ 10: Nakamura T, Sato M, Kakinuma H, Miyata N, Taniguchi K, Bando K, Koda A, Kameo K. [Related Articles](#), [Links](#)
-  Pyrazole and isoxazole derivatives as new, potent, and selective 20-hydroxy-5,8,11,14-eicosatetraenoic acid synthase inhibitors.  
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Hypertension. 2003 Oct;42(4):669-73. Epub 2003 Jul 21.  
PMID: 12874093 [PubMed - indexed for MEDLINE]

- ☐ **12:** Cambj-Sapunar L, Yu M, Harder DR, Roman RJ. [Related Articles](#), [Links](#)



Contribution of 5-hydroxytryptamine1B receptors and 20-hydroxyeicosatetraenoic acid to fall in cerebral blood flow after subarachnoid hemorrhage.

Stroke. 2003 May;34(5):1269-75. Epub 2003 Apr 3.

PMID: 12677022 [PubMed - indexed for MEDLINE]

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NO inhibits Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransport via a cytochrome P-450-dependent pathway in renal epithelial cells (MMDD1).

Am J Physiol Renal Physiol. 2003 Jun;284(6):F1235-44. Epub 2003 Feb 11.

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Am J Physiol Heart Circ Physiol. 2003 May;284(5):H1528-35.

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 Discovery of a N'-hydroxyphenylformamidine derivative HET0016 as a potent and selective 20-HETE synthase inhibitor. Bioorg Med Chem Lett. 2001 Dec 3;11(23):2993-5. PMID: 11714595 [PubMed - indexed for MEDLINE]

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 Role of guanylyl cyclase and cytochrome P-450 on renal response to nitric oxide. Am J Physiol Renal Physiol. 2001 Sep;281(3):F420-7. PMID: 11502591 [PubMed - indexed for MEDLINE]

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 HET0016, a potent and selective inhibitor of 20-HETE synthesizing enzyme. Br J Pharmacol. 2001 Jun;133(3):325-9. PMID: 11375247 [PubMed - indexed for MEDLINE]

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=> S HET0016

L1 86 HET0016

=> S HETE (4A) (arachidonic acid)

L2 1275 HETE (4A) (ARACHIDONIC ACID)

=> s l1 (8A) l2

L3 5 L1 (8A) L2

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AN   2003:258659   BIOSIS  
DN   PREV200300258659  
TI   CYP4A isoform inhibitory profile of HET0016, a selective  
inhibitor of  
      20-HETE synthesis.  
AU   Seki, Takayuki [Reprint Author]; Wang, Mong-Heng; Miyata,  
Noriyuki;  
      Laniado-Schwartzman, Michal  
CS   Medicinal Research Laboratories, TAISHO PHARMACEUTICAL CO.,  
LTD., 1-403  
      Yoshino-cho, Saitama City, Saitama, 330-8530, Japan  
      takayuki.seki@po.rd.taisho.co.jp; mong-heng\_wang@nymc.edu;  
      noriyuki.miyata@po.rd.taisho.co.jp; michal\_schwartzman@nymc.edu  
SO   FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No.  
90.8.  
      <http://www.fasebj.org/>. e-file.  
      Meeting Info.: FASEB Meeting on Experimental Biology:  
Translating the  
      Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.  
      ISSN: 0892-6638 (ISSN print).  
DT   Conference; (Meeting)  
      Conference; Abstract; (Meeting Abstract)  
LA   English  
ED   Entered STN: 4 Jun 2003  
      Last Updated on STN: 4 Jun 2003  
AB   20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) is a potent  
      vasoconstrictor eicosanoid in the renal and cerebral  
microcirculation. We  
      have previously reported that HET0016 (N-hydroxy-N'-(4-butyl-2-  
      methylphenyl)-formamidine) is a potent and selective inhibitor  
of 20-HETE  
      synthesis in rat and human renal microsomes (Br. J.  
Pharmacol.135:325,  
      2001). In the present study, we examined the effect of HET0016  
on 20-HETE  
      synthesis catalyzed by recombinant CYP4A1, 4A2, and 4A3 and  
characterized  
      the enzyme inhibitory profile of HET0016. **HET0016** inhibited  
**arachidonic acid** (AA) conversion to 20-**HETE** by



all three CYP4A isoforms in a concentration-dependent manner.  
The IC50 values of HET0016 for recombinant CYP4A1, 4A2, and 4A3-catalyzed 20-HETE syntheses averaged 17.7 nM, 12.1 nM, and 20.6 nM, respectively.  
Formation of 20-HETE from AA by recombinant CYP4A1 exhibited simple Michaelis-Menten kinetics. The Ki value of HET0016 for CYP4A1 was 18.6 nM.  
Furthermore the plot of maximal initial velocity (Vmax) versus the amount of enzyme added showed that HET0016 is an irreversible inhibitor. These results indicate that HET0016 is a non-competitive and irreversible inhibitor of CYP4A family and thereby may be used to specifically target the 20-HETE synthesis in vitro and in vivo.

L4 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1  
AN 2001668726 MEDLINE  
DN PubMed ID: 11714595  
TI Discovery of a N'-hydroxyphenylformamidine derivative HET0016 as a potent and selective 20-HETE synthase inhibitor.  
AU Sato M; Ishii T; Kobayashi-Matsunaga Y; Amada H; Taniguchi K; Miyata N; Kameo K  
CS Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Saitama, Saitama 330-8530, Japan.  
SO Bioorganic & medicinal chemistry letters, (2001 Dec 3) Vol. 11, No. 23, pp. 2993-5.  
Journal code: 9107377. ISSN: 0960-894X.  
CY England: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200203  
ED Entered STN: 20011121  
Last Updated on STN: 20020307  
Entered Medline: 20020305  
AB N-(4-Butyl-2-methylphenyl)-N'-hydroxyformamidine (HET0016) was evaluated as the first potent and selective inhibitor of 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) synthase. The IC(50) value of **HET0016** for the production of 20-**HETE** from **arachidonic acid** (AA) by human renal microsomes was 8.9+/-2.7 nM, with over 200 times the selectivity of xenobiotic-

metabolizing cytochrome P450 enzymes. An examination of the structure-activity relationship revealed that the unsubstituted hydroxyformamidine moiety and the substituent at the para-position of the N-hydroxyformamidine moiety are necessary for the potent activity of HET0016.

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L6 ANSWER 1 OF 5 MEDLINE on STN  
AN 2006163135 IN-PROCESS  
DN PubMed ID: 16352703  
TI 9L Gliosarcoma Cell Proliferation and Tumor Growth in Rats Are Suppressed  
by N-Hydroxy-N'-(4-butyl-2-methylphenol) Formamidine (HET0016), a Selective Inhibitor of CYP4A.  
AU Guo Meng; Roman Richard J; Fenstermacher Joseph D; Brown Stephen L; Falck  
John R; Arbab Ali S; Edwards Paul A; Scicli A Guillermo  
CS Eye Care Services, Henry Ford Hospital, One Ford Place, 4 D, Detroit, MI  
48202-3450.. mguo1@hfhs.org  
SO The Journal of pharmacology and experimental therapeutics, (2006 Apr) Vol.  
317, No. 1, pp. 97-108. Electronic Publication: 2005-12-13.  
Journal code: 0376362. ISSN: 0022-3565.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals  
ED Entered STN: 20060323  
Last Updated on STN: 20060323

AB The present study examined the effects of N-hydroxy-N'-(4-butyl-2-methylphenyl) formamidine (**HET0016**), a selective inhibitor of the formation of 20-hydroxyeicosatrienoic acid (20-HETE) on the growth of

9L rat gliosarcoma cells in vitro and in vivo. After 48 h of incubation,

**HET0016** reduced the proliferation of 9L in vitro by 55%, and this was associated with a fall in p42/p44 mitogen-activated protein kinase and

stress-activated protein kinase/c-Jun NH(2)-terminal kinase phosphorylation and increased apoptosis. **HET0016** inhibited epidermal growth factor (EGF) and platelet-derived growth factor (PDGF)-induced proliferation and diminished phosphorylation of PDGF

receptors. A stable 20-HETE analog increased 9L cell proliferation. In

vivo, chronic administration of **HET0016** (10 mg/kg/day i.p.) for 2 weeks reduced the volume of 9L tumors by 80%. This was accompanied by a

4-fold reduction in the mitotic index, a 3- to 4-fold increase in the

apoptotic index, and a approximately 50% decrease in vascularization in

the tumor. **HET0016** treatment increased mean survival time of the animals from 17 to 22 days. Liquid chromatography/mass spectrometry

experiments indicated that neither 9L cells grown in vitro nor 9L tumors

removed produce 20-**HETE** when incubated with **arachidonic acid**. The normal surrounding brain tissue, however, avidly makes 20-HETE, and this activity is selectively inhibited by **HET0016**. These results suggest that **HET0016** may be the prototype of a class of antigrowth compounds that may be efficacious for treating

malignant brain tumors. In vivo, it may act in part by inhibiting the

formation of 20-HETE by the surrounding tissue. However, the antiproliferative effects of **HET0016** on 9L cells in vitro seem unrelated to its ability to inhibit the formation of 20-HETE.

L6 ANSWER 2 OF 5 MEDLINE on STN DUPLICATE 1

AN 2005560419 MEDLINE

DN PubMed ID: 16081682

TI Human U251 glioma cell proliferation is suppressed by **HET0016** [N-hydroxy-N'-(4-butyl-2-methylphenyl)formamidine], a selective inhibitor of CYP4A.

AU Guo Meng; Roman Richard J; Falck John R; Edwards Paul A; Scicli A Guillermo

CS Eye Care Services, Henry Ford Hospital, Detroit, MI 48202-3450, USA..

mguo1@hfhs.org

NC EY014385 (NEI)  
 GM31278 (NIGMS)  
 HL 036279 (NHLBI)  
 SO The Journal of pharmacology and experimental therapeutics, (2005  
 Nov) Vol.  
 315, No. 2, pp. 526-33. Electronic Publication: 2005-08-04.  
 Journal code: 0376362. ISSN: 0022-3565.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200601  
 ED Entered STN: 20051021  
 Last Updated on STN: 20060113  
 Entered Medline: 20060112  
 AB We have previously reported that **HET0016** [N-hydroxy-N'-(4-butyl-  
 2 methylphenyl)formamidine], a selective inhibitor of CYP4A and  
 thus  
 20-HETE (20-hydroxyeicosatetraenoic acid) synthesis, inhibits  
 endothelial  
 cell proliferation and decreases angiogenesis induced by human  
 glioma cell  
 U251. A stable 20-HETE agonist, WIT003  
 [20-hydroxyeicosa-5(Z),14(Z)-  
 dienoic acid (1 microm)], increased U251 cell proliferation from  
 3.9- to  
 4.8-folds from T(0) (time of the treatment). We examined the  
 effects of  
**HET0016** on the growth of U251. **HET0016** inhibited U251  
 basal cell proliferation in a dose-dependent manner. 10 microm  
**HET0016** suppressed 56% of U251 proliferation and significantly  
 increased the proportions of the cells arrested in the G(0)/G(1)  
 phase of  
 the cell cycle. Exposure to **HET0016** (as early as 4 h) reduced  
 protein tyrosine and p42/p44 MAPK (mitogen-activated protein  
 kinase)  
 phosphorylation. Furthermore, **HET0016** significantly inhibited  
 the U251 proliferation and phosphorylation of both the epidermal  
 growth  
 factor (EGF) receptor and p42/p44 MAPK induced by EGF. CYP4A  
 mRNA and  
 proteins were both present in U251. This suggests that **HET0016**  
 inhibited U251 proliferation by inhibiting 20-HETE synthesis.  
 However,  
 U251 did not synthesize 20-**HETE** in the presence of  
**arachidonic acid**. This implies that **HET0016**  
 suppresses U251 proliferation by mechanisms that are not yet  
 clear but may  
 involve activities other than inhibition of 20-HETE synthesis.  
 We  
 concluded that **HET0016** may be the prototype of novel compounds  
 that suppress human glioma cell proliferation.

L6 ANSWER 3 OF 5 MEDLINE on STN DUPLICATE 2  
 AN 2003463360 MEDLINE  
 DN PubMed ID: 12874093  
 TI Inhibitors of 20-HETE formation promote salt-sensitive hypertension in rats.  
 AU Hoagland Kimberly M; Flasch Averia K; Roman Richard J  
 CS Department of Physiology, Medical College of Wisconsin, Milwaukee, WI 53226, USA.  
 NC HL-10364-03 (NHLBI)  
 HL-29574 (NHLBI)  
 HL-36279 (NHLBI)  
 SO Hypertension, (2003 Oct) Vol. 42, No. 4, pp. 669-73. Electronic Publication: 2003-07-21. Journal code: 7906255. E-ISSN: 1524-4563.  
 CY United States  
 DT (LECTURES)  
 LA English  
 FS Priority Journals  
 EM 200311  
 ED Entered STN: 20031004  
 Last Updated on STN: 20031111  
 Entered Medline: 20031110  
 AB This study examined whether chronic blockade of epoxyeicosatrienoic acids (EETs) and/or 20-hydroxyeicosatetraenoic acid (20-HETE) formation promotes development of salt-sensitive hypertension. Changes in blood pressure, renal cytochrome P450 metabolism of arachidonic acid, and 20-HETE excretion in response to a high salt diet were measured in rats chronically treated with 1-aminobenzotriazole (ABT, 50 mg/kg per day) to block EETs and 20-HETE formation or N-hydroxy-N'-(4-butyl-2 methylphenyl) formamidine (HET0016, 10 mg/kg per day) that selectively reduces 20-HETE formation. ABT reduced blood pressure in rats fed a low salt (0.4% NaCl) diet, but blood pressure rose by 20 mm Hg after these rats were switched to a high salt (8% NaCl) diet for 10 days. HET0016 had no effect on blood pressure in rats fed a low salt diet; however, blood pressure rose by 18 mm Hg after the rats were fed a high salt diet. 20-HETE formation in kidney homogenates rose by 30% and epoxygenase activity doubled when rats were fed a high salt diet. Chronic treatment with ABT and HET0016 inhibited the renal formation of

20-HETE by approximately 90%. Renal epoxygenase activity decreased by 76%

in ABT-treated rats and was not significantly altered in rats treated with

**HET0016**. 20-HETE excretion rose from 470+/-21 to 570+/-41 ng/d when the rats were switched from the low to the high salt diet. 20-HETE

excretion fell by 68% and 85% in rats that were chronically treated with

ABT and **HET0016**. These results suggest that chronic blockade of the formation of 20-HETE promotes the development of salt-sensitive hypertension in rats.

L6 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2003:258659 BIOSIS

DN PREV200300258659

TI CYP4A isoform inhibitory profile of **HET0016**, a selective inhibitor of 20-HETE synthesis.

AU Seki, Takayuki [Reprint Author]; Wang, Mong-Heng; Miyata, Noriyuki;

Laniado-Schwartzman, Michal

CS Medicinal Research Laboratories, TAISHO PHARMACEUTICAL CO., LTD., 1-403

Yoshino-cho, Saitama City, Saitama, 330-8530, Japan

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noriyuki.miyata@po.rd.taisho.co.jp; michal\_schwartzman@nymc.edu

SO FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 90.8.

<http://www.fasebj.org/>. e-file.

Meeting Info.: FASEB Meeting on Experimental Biology:

Translating the

Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.

ISSN: 0892-6638 (ISSN print).

DT Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 4 Jun 2003

Last Updated on STN: 4 Jun 2003

AB 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) is a potent vasoconstrictor eicosanoid in the renal and cerebral microcirculation. We

have previously reported that **HET0016** (N-hydroxy-N'-(4-butyl-2-methylphenyl)-formamidine) is a potent and selective inhibitor of 20-HETE

synthesis in rat and human renal microsomes (Br. J. Pharmacol. 135:325,

2001). In the present study, we examined the effect of **HET0016** on 20-HETE synthesis catalyzed by recombinant CYP4A1, 4A2, and 4A3 and

characterized the enzyme inhibitory profile of **HET0016**.

**HET0016** inhibited **arachidonic acid** (AA) conversion to 20-**HETE** by all three CYP4A isoforms in a concentration-dependent manner. The IC<sub>50</sub> values of **HET0016** for recombinant CYP4A1, 4A2, and 4A3-catalyzed 20-HETE syntheses averaged 17.7 nM, 12.1 nM, and 20.6 nM, respectively. Formation of 20-HETE from AA by recombinant CYP4A1 exhibited simple Michaelis-Menten kinetics. The K<sub>i</sub> value of **HET0016** for CYP4A1 was 18.6 nM. Furthermore the plot of maximal initial velocity (V<sub>max</sub>) versus the amount of enzyme added showed that **HET0016** is an irreversible inhibitor. These results indicate that **HET0016** is a non-competitive and irreversible inhibitor of CYP4A family and thereby may be used to specifically target the 20-HETE synthesis in vitro and in vivo.

L6 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 3  
 AN 2001668726 MEDLINE  
 DN PubMed ID: 11714595  
 TI Discovery of a N'-hydroxyphenylformamidine derivative **HET0016** as a potent and selective 20-HETE synthase inhibitor.  
 AU Sato M; Ishii T; Kobayashi-Matsunaga Y; Amada H; Taniguchi K; Miyata N; Kameo K  
 CS Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Saitama, Saitama 330-8530, Japan.  
 SO Bioorganic & medicinal chemistry letters, (2001 Dec 3) Vol. 11, No. 23, pp. 2993-5.  
 Journal code: 9107377. ISSN: 0960-894X.  
 CY England: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200203  
 ED Entered STN: 20011121  
 Last Updated on STN: 20020307  
 Entered Medline: 20020305  
 AB N-(4-Butyl-2-methylphenyl)-N'-hydroxyformamidine (**HET0016**) was evaluated as the first potent and selective inhibitor of 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) synthase. The IC<sub>50</sub> value of **HET0016** for the production of 20-**HETE** from **arachidonic acid** (AA) by human renal microsomes was 8.9+/-2.7 nM, with over 200 times the selectivity of xenobiotic-metabolizing cytochrome P450 enzymes. An examination of the structure-activity relationship revealed that the unsubstituted hydroxyformamidine moiety and the substituent at the para-position of the

N-hydroxyformamidine moiety are necessary for the potent activity of  
**HET0016.**



=> s Formamidine  
L7 4165 FORMAMIDINE

=> s 17 (8A) 12  
L8 0 L7 (8A) L2

=> s 17 and 12  
L9 13 L7 AND L2

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L10 ANSWER 1 OF 6 MEDLINE on STN  
AN 2006163135 IN-PROCESS  
DN PubMed ID: 16352703  
TI 9L Gliosarcoma Cell Proliferation and Tumor Growth in Rats Are  
Suppressed  
by N-Hydroxy-N'-(4-butyl-2-methylphenol) **Formamidine** (HET0016),  
a Selective Inhibitor of CYP4A.  
AU Guo Meng; Roman Richard J; Fenstermacher Joseph D; Brown Stephen  
L; Falck  
John R; Arbab Ali S; Edwards Paul A; Scicli A Guillermo  
CS Eye Care Services, Henry Ford Hospital, One Ford Place, 4 D,  
Detroit, MI  
48202-3450.. mguo1@hfhs.org  
SO The Journal of pharmacology and experimental therapeutics, (2006  
Apr) Vol.  
317, No. 1, pp. 97-108. Electronic Publication: 2005-12-13.  
Journal code: 0376362. ISSN: 0022-3565.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority  
Journals  
ED Entered STN: 20060323  
Last Updated on STN: 20060323  
AB The present study examined the effects of N-hydroxy-N'-(4-butyl-2  
methylphenyl) **formamidine** (HET0016), a selective inhibitor of

the formation of 20-hydroxyeicosatrienoic acid (20-HETE) on the growth of 9L rat gliosarcoma cells in vitro and in vivo. After 48 h of incubation, HET0016 reduced the proliferation of 9L in vitro by 55%, and this was associated with a fall in p42/p44 mitogen-activated protein kinase and stress-activated protein kinase/c-Jun NH(2)-terminal kinase phosphorylation and increased apoptosis. HET0016 inhibited epidermal growth factor (EGF) and platelet-derived growth factor (PDGF)-induced proliferation and diminished phosphorylation of PDGF receptors. A stable 20-HETE analog increased 9L cell proliferation. In vivo, chronic administration of HET0016 (10 mg/kg/day i.p.) for 2 weeks reduced the volume of 9L tumors by 80%. This was accompanied by a 4-fold reduction in the mitotic index, a 3- to 4-fold increase in the apoptotic index, and a approximately 50% decrease in vascularization in the tumor. HET0016 treatment increased mean survival time of the animals from 17 to 22 days. Liquid chromatography/mass spectrometry experiments indicated that neither 9L cells grown in vitro nor 9L tumors removed produce 20-HETE when incubated with **arachidonic acid**. The normal surrounding brain tissue, however, avidly makes 20-HETE, and this activity is selectively inhibited by HET0016. These results suggest that HET0016 may be the prototype of a class of antigrowth compounds that may be efficacious for treating malignant brain tumors. In vivo, it may act in part by inhibiting the formation of 20-HETE by the surrounding tissue. However, the antiproliferative effects of HET0016 on 9L cells in vitro seem unrelated to its ability to inhibit the formation of 20-HETE.

L10 ANSWER 2 OF 6 MEDLINE on STN DUPLICATE 1  
 AN 2005560419 MEDLINE  
 DN PubMed ID: 16081682  
 TI Human U251 glioma cell proliferation is suppressed by HET0016 [N-hydroxy-N'-(4-butyl-2-methylphenyl)**formamidine**], a selective inhibitor of CYP4A.  
 AU Guo Meng; Roman Richard J; Falck John R; Edwards Paul A; Scicli A

Guillermo  
CS Eye Care Services, Henry Ford Hospital, Detroit, MI 48202-3450,  
USA..  
mguol@hfhs.org  
NC EY014385 (NEI)  
GM31278 (NIGMS)  
HL 036279 (NHLBI)  
SO The Journal of pharmacology and experimental therapeutics, (2005  
Nov) Vol.  
315, No. 2, pp. 526-33. Electronic Publication: 2005-08-04.  
Journal code: 0376362. ISSN: 0022-3565.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200601  
ED Entered STN: 20051021  
Last Updated on STN: 20060113  
Entered Medline: 20060112  
AB We have previously reported that HET0016 [N-hydroxy-N'-(4-butyl-2  
methylphenyl)**formamidine**], a selective inhibitor of CYP4A and  
thus 20-HETE (20-hydroxyeicosatetraenoic acid) synthesis,  
inhibits  
endothelial cell proliferation and decreases angiogenesis  
induced by human  
glioma cell U251. A stable 20-HETE agonist, WIT003  
[20-hydroxyeicosa-  
5(Z),14(Z)-dienoic acid (1 microM)], increased U251 cell  
proliferation  
from 3.9- to 4.8-folds from T(0) (time of the treatment). We  
examined the  
effects of HET0016 on the growth of U251. HET0016 inhibited  
U251 basal  
cell proliferation in a dose-dependent manner. 10 microM HET0016  
suppressed 56% of U251 proliferation and significantly increased  
the  
proportions of the cells arrested in the G(0)/G(1) phase of the  
cell  
cycle. Exposure to HET0016 (as early as 4 h) reduced protein  
tyrosine and  
p42/p44 MAPK (mitogen-activated protein kinase) phosphorylation.  
Furthermore, HET0016 significantly inhibited the U251  
proliferation and  
phosphorylation of both the epidermal growth factor (EGF)  
receptor and  
p42/p44 MAPK induced by EGF. CYP4A mRNA and proteins were both  
present in  
U251. This suggests that HET0016 inhibited U251 proliferation by  
inhibiting 20-HETE synthesis. However, U251 did not synthesize  
20-  
**HETE** in the presence of **arachidonic acid**.  
This implies that HET0016 suppresses U251 proliferation by  
mechanisms that

are not yet clear but may involve activities other than inhibition of 20-HETE synthesis. We concluded that HET0016 may be the prototype of novel compounds that suppress human glioma cell proliferation.

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AN 2005507378 EMBASE

TI Role of 20-hydroxyeicosatetraenoic acid (20-HETE) in vascular system.

AU Miyata N.; Roman R.J.

CS Dr. N. Miyata, Medicinal Pharmacology Laboratory, Medicinal Research

Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Saitama-city, Saitama 331-9530, Japan.

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SO Journal of Smooth Muscle Research, (2005) Vol. 41, No. 4, pp. 175-193. .

Refs: 116

ISSN: 0916-8737 CODEN: JSMRE2

CY Japan

DT Journal; General Review

FS 018 Cardiovascular Diseases and Cardiovascular Surgery

030 Pharmacology

037 Drug Literature Index

LA English

SL English

ED Entered STN: 20051208

Last Updated on STN: 20051208

AB Cytochrome P450s (P450) metabolize **arachidonic acid** (AA) to hydroxyeicosatetraenoic acids (**HETEs**) and epoxyeicosatrienoic acids (EETs). Among these eicosanoids, 20-HETE is

formed in a tissue and cell-specific fashion and plays an important role

in the regulation of vascular tone in the brain, kidney, heart and

splanchnic beds. 20-HETE is a potent vasoconstrictor produced in vascular

smooth muscle (VSM) cells. It depolarizes VSM by blocking the open-state

probability of  $\text{Ca}^{2+}$ -activated  $\text{K}^{+}$ -channels. Inhibitors of the

formation of 20-HETE block the myogenic response of renal and cerebral

arterioles in vitro and autoregulation of renal and cerebral blood flow in

vivo. The formation of 20-HETE in vascular smooth muscle is stimulated by

angiotensin II, endothelin and norepinephrine and is inhibited by nitric

oxide (NO). 20-HETE also stimulates mitogenic and angiogenic responses in vitro and in vivo. Changes in the production of 20-HETE have been observed in ischemic cerebrovascular diseases, cardiac ischemia-reperfusion injury, kidney diseases, hypertension, diabetes, uremia, toxemia of pregnancy. The physiological and pathophysiological role of 20-HETE in the regulation of vascular tone are being revealed by the use of newly developed inhibitors of the synthesis of 20-HETE and 20-HETE analogs. The present review summarizes recent findings implicating a critical role for 20-HETE in altering cardiovascular function in a variety of pathological conditions.

L10 ANSWER 4 OF 6 MEDLINE on STN DUPLICATE 2  
 AN 2003463360 MEDLINE  
 DN PubMed ID: 12874093  
 TI Inhibitors of 20-HETE formation promote salt-sensitive hypertension in rats.  
 AU Hoagland Kimberly M; Flasch Averia K; Roman Richard J  
 CS Department of Physiology, Medical College of Wisconsin, Milwaukee, WI 53226, USA.  
 NC HL-10364-03 (NHLBI)  
 HL-29574 (NHLBI)  
 HL-36279 (NHLBI)  
 SO Hypertension, (2003 Oct) Vol. 42, No. 4, pp. 669-73. Electronic Publication: 2003-07-21.  
 Journal code: 7906255. E-ISSN: 1524-4563.  
 CY United States  
 DT (LECTURES)  
 LA English  
 FS Priority Journals  
 EM 200311  
 ED Entered STN: 20031004  
 Last Updated on STN: 20031111  
 Entered Medline: 20031110  
 AB This study examined whether chronic blockade of epoxyeicosatrienoic acids (EETs) and/or 20-hydroxyeicosatetraenoic acid (20-HETE) formation promotes development of salt-sensitive hypertension. Changes in blood pressure, renal cytochrome P450 metabolism of arachidonic acid, and 20-HETE excretion in response to a high salt diet were measured in rats chronically treated with 1-aminobenzotriazole (ABT, 50

mg/kg per day) to block EETs and 20-HETE formation or N-hydroxy-N'-(4-butyl-2 methylphenyl) **formamidine** (HET0016, 10 mg/kg per day) that selectively reduces 20-HETE formation. ABT reduced blood pressure in rats fed a low salt (0.4% NaCl) diet, but blood pressure rose by 20 mm Hg after these rats were switched to a high salt (8% NaCl) diet for 10 days. HET0016 had no effect on blood pressure in rats fed a low salt diet; however, blood pressure rose by 18 mm Hg after the rats were fed a high salt diet. 20-HETE formation in kidney homogenates rose by 30% and epoxygenase activity doubled when rats were fed a high salt diet. Chronic treatment with ABT and HET0016 inhibited the renal formation of 20-HETE by approximately 90%. Renal epoxygenase activity decreased by 76% in ABT-treated rats and was not significantly altered in rats treated with HET0016. 20-HETE excretion rose from 470+/-21 to 570+/-41 ng/d when the rats were switched from the low to the high salt diet. 20-HETE excretion fell by 68% and 85% in rats that were chronically treated with ABT and HET0016. These results suggest that chronic blockade of the formation of 20-HETE promotes the development of salt-sensitive hypertension in rats.

L10 ANSWER 5 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2003:258659 BIOSIS

DN PREV200300258659

TI CYP4A isoform inhibitory profile of HET0016, a selective inhibitor of

20-HETE synthesis.

AU Seki, Takayuki [Reprint Author]; Wang, Mong-Heng; Miyata, Noriyuki;

Laniado-Schwartzman, Michal

CS Medicinal Research Laboratories, TAISHO PHARMACEUTICAL CO., LTD., 1-403

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noriyuki.miyata@po.rd.taisho.co.jp; michal\_schwartzman@nymc.edu

SO FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 90.8.

<http://www.fasebj.org/>. e-file.

Meeting Info.: FASEB Meeting on Experimental Biology:  
Translating the

Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.  
ISSN: 0892-6638 (ISSN print).

DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 4 Jun 2003

Last Updated on STN: 4 Jun 2003

AB 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) is a potent  
vasoconstrictor eicosanoid in the renal and cerebral  
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have previously reported that HET0016 (N-hydroxy-N'-(4-butyl-2-  
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Pharmacol.135:325, 2001). In the present study, we examined the  
effect of

HET0016 on 20-HETE synthesis catalyzed by recombinant CYP4A1,  
4A2, and 4A3

and characterized the enzyme inhibitory profile of HET0016.

HET0016

inhibited **arachidonic acid** (AA) conversion to 20-

**HETE** by all three CYP4A isoforms in a concentration-dependent  
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4A3-catalyzed 20-HETE syntheses averaged 17.7 nM, 12.1 nM, and  
20.6 nM,

respectively. Formation of 20-HETE from AA by recombinant CYP4A1  
exhibited simple Michaelis-Menten kinetics. The Ki value of

HET0016 for

CYP4A1 was 18.6 nM. Furthermore the plot of maximal initial  
velocity

(Vmax) versus the amount of enzyme added showed that HET0016 is  
an

irreversible inhibitor. These results indicate that HET0016 is a  
non-competitive and irreversible inhibitor of CYP4A family and  
thereby may

be used to specifically target the 20-HETE synthesis in vitro  
and in vivo.

L10 ANSWER 6 OF 6 MEDLINE on STN

DUPLICATE 3

AN 2001668726 MEDLINE

DN PubMed ID: 11714595

TI Discovery of a N'-hydroxyphenylformamidine derivative HET0016 as  
a potent  
and selective 20-HETE synthase inhibitor.

AU Sato M; Ishii T; Kobayashi-Matsunaga Y; Amada H; Taniguchi K;  
Miyata N;

Kameo K

CS Medicinal Research Laboratories, Taisho Pharmaceutical Co.,  
Ltd., 1-403

Yoshino-cho, Saitama, Saitama 330-8530, Japan.

SO Bioorganic & medicinal chemistry letters, (2001 Dec 3) Vol. 11,  
No. 23,  
pp. 2993-5.

Journal code: 9107377. ISSN: 0960-894X.

CY England: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200203

ED Entered STN: 20011121

Last Updated on STN: 20020307

Entered Medline: 20020305

AB N-(4-Butyl-2-methylphenyl)-N'-hydroxyformamidine (HET0016) was  
evaluated

as the first potent and selective inhibitor of  
20-hydroxy-5,8,11,14-  
eicosatetraenoic acid (20-HETE) synthase. The IC(50) value of  
HET0016 for  
the production of 20-**HETE** from **arachidonic**  
**acid** (AA) by human renal microsomes was 8.9+/-2.7 nM, with over  
200 times the selectivity of xenobiotic-metabolizing cytochrome

P450  
enzymes. An examination of the structure-activity relationship  
revealed

that the unsubstituted hydroxyformamidine moiety and the  
substituent at

the para-position of the N-hydroxyformamidine moiety are  
necessary for the  
potent activity of HET0016.

=>





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☐ 9L Gliosarcoma Cell Proliferation and Tumor Growth in Rats Are Suppressed by N-Hydroxy-N'-(4-butyl-2-methylphenol) Formamidine (HET0016), a Selective Inhibitor of CYP4A. J Pharmacol Exp Ther. 2006 Apr;317(1):97-108. Epub 2005 Dec 13. PMID: 16352703 [PubMed - in process]

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☐ 3: Seki T, Wang MH, Miyata N, Laniado-Schwartzman M.

Related Articles, Links

☐ Cytochrome P450 4A isoform inhibitory profile of N-hydroxy-N'-(4-butyl-2-methylphenyl)-formamidine (HET0016), a selective inhibitor of 20-HETE synthesis. Biol Pharm Bull. 2005 Sep;28(9):1651-4. PMID: 16141533 [PubMed - indexed for MEDLINE]

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☐ 4: Guo M, Roman RJ, Falck JR, Edwards PA, Scicli AG.

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☐ Human U251 glioma cell proliferation is suppressed by HET0016 [N-hydroxy-N'-(4-butyl-2-methylphenyl)formamidine], a selective inhibitor of CYP4A. J Pharmacol Exp Ther. 2005 Nov;315(2):526-33. Epub 2005 Aug 4. PMID: 16081682 [PubMed - indexed for MEDLINE]

☐ 5: Chen P, Guo M, Wygle D, Edwards PA, Falck JR, Roman RJ, Scicli AG.

Related Articles, Links

-  Inhibitors of cytochrome P450 4A suppress angiogenic responses.  
Am J Pathol. 2005 Feb;166(2):615-24.  
PMID: 15681843 [PubMed - indexed for MEDLINE]
- ☐ 6: [Jiang M](#), [Mezentsev A](#), [Kemp R](#), [Byun K](#), [Falck JR](#), [Miano JM](#), [Nasjletti A](#), [Abraham NG](#), [Laniado-Schwartzman M](#). Related Articles, Links
-  Smooth muscle--specific expression of CYP4A1 induces endothelial sprouting in renal arterial microvessels.  
Circ Res. 2004 Feb 6;94(2):167-74. Epub 2003 Dec 11.  
PMID: 14670847 [PubMed - indexed for MEDLINE]
- ☐ 7: [Hoagland KM](#), [Flasch AK](#), [Roman RJ](#). Related Articles, Links
-  Inhibitors of 20-HETE formation promote salt-sensitive hypertension in rats.  
Hypertension. 2003 Oct;42(4):669-73. Epub 2003 Jul 21.  
PMID: 12874093 [PubMed - indexed for MEDLINE]
- ☐ 8: [Amaral SL](#), [Maier KG](#), [Schipper DN](#), [Roman RJ](#), [Greene AS](#). Related Articles, Links
-  CYP4A metabolites of arachidonic acid and VEGF are mediators of skeletal muscle angiogenesis.  
Am J Physiol Heart Circ Physiol. 2003 May;284(5):H1528-35. Epub 2003 Jan 9.  
PMID: 12521947 [PubMed - indexed for MEDLINE]
- ☐ 9: [Sato M](#), [Ishii T](#), [Kobayashi-Matsunaga Y](#), [Amada H](#), [Taniguchi K](#), [Miyata N](#), [Kameo K](#). Related Articles, Links
-  Discovery of a N'-hydroxyphenylformamidine derivative HET0016 as a potent and selective 20-HETE synthase inhibitor.  
Bioorg Med Chem Lett. 2001 Dec 3;11(23):2993-5.  
PMID: 11714595 [PubMed - indexed for MEDLINE]
- ☐ 10: [Miyata N](#), [Taniguchi K](#), [Seki T](#), [Ishimoto T](#), [Sato-Watanabe M](#), [Yasuda Y](#), [Doi M](#), [Kametani S](#), [Tomishima Y](#), [Ueki T](#), [Sato M](#), [Kameo K](#). Related Articles, Links
-  HET0016, a potent and selective inhibitor of 20-HETE synthesizing enzyme.  
Br J Pharmacol. 2001 Jun;133(3):325-9.  
PMID: 11375247 [PubMed - indexed for MEDLINE]

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☐ 1: [Miyata N, Seki T, Tanaka Y, Omura T, Taniguchi K, Doi M, Bandou K, Kametani S, Sato M, Okuyama S, Cambj-Sapunar L, Harder DR, Roman RJ.](#) [Related Articles, Links](#)

☐ Beneficial effects of a new 20-hydroxyeicosatetraenoic acid synthesis inhibitor, TS-011 [N-(3-chloro-4-morpholin-4-yl) phenyl-N'-hydroxyimido formamide], on hemorrhagic and ischemic stroke. J Pharmacol Exp Ther. 2005 Jul;314(1):77-85. Epub 2005 Apr 14. PMID: 15831442 [PubMed - indexed for MEDLINE]

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L2	0	cyp4a11 near4 inhibitor	USPAT	OR	OFF	2006/03/27 16:53

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NEWS 6	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements
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		INPADOC
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NEWS 11	FEB 21	STN AnaVist, Version 1.1, lets you share your STN
AnaVist		
		visualization results
NEWS 12	FEB 22	Status of current WO (PCT) information on STN
NEWS 13	FEB 22	The IPC thesaurus added to additional patent
databases on STN		
NEWS 14	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 15	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 16	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS 17	FEB 28	TOXCENTER reloaded with enhancements
NEWS 18	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental
spectral		
		property data
NEWS 19	MAR 01	INSPEC reloaded and enhanced
NEWS 20	MAR 03	Updates in PATDPA; addition of IPC 8 data without
attributes		
NEWS 21	MAR 08	X.25 communication option no longer available after
June 2006		

NEWS 22 MAR 22 EMBASE is now updated on a daily basis

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,  
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.  
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=> File Medline EMBASE Biosis Caplus  
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=> s cyp4a11 (4a) inhibitor  
L1 0 CYP4A11 (4A) INHIBITOR

=> s cyp4a-11 (4a) inhibitor  
L2 0 CYP4A-11 (4A) INHIBITOR



## EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	wo-9943310-\$.did.	USPAT	OR	OFF	2006/03/27 16:53
L2	0	cyp4a11 near4 inhibitor	USPAT	OR	OFF	2006/03/27 17:36
L3	0	CYP4a11 near4 HETE	USPAT	OR	OFF	2006/03/27 17:36
L4	0	CYP4a11 near4 (arachidonic adj acid)	USPAT	OR	OFF	2006/03/27 17:37
L5	0	CYP4F near4 (arachidonic adj acid)	USPAT	OR	OFF	2006/03/27 17:37
L6	0	CYP4F near4 (hete)	USPAT	OR	OFF	2006/03/27 17:37

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	DEC 21	IPC search and display fields enhanced in CA/Caplus
with the		
		IPC reform
NEWS 4	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in
USPATFULL/		
		USPAT2
NEWS 5	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 6	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements
added to		
		INPADOC
NEWS 7	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 8	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 9	JAN 30	Saved answer limit increased
NEWS 10	JAN 31	Monthly current-awareness alert (SDI) frequency
		added to TULSA
NEWS 11	FEB 21	STN AnaVist, Version 1.1, lets you share your STN
AnaVist		
		visualization results
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=> s CYP4a11 (4A) HETE  
L1 8 CYP4A11 (4A) HETE

=> s CYP4a11 (4A) (arachidonic acid)  
L2 13 CYP4A11 (4A) (ARACHIDONIC ACID)

=> s l1 and l2  
L3 5 L1 AND L2

=> duplicate  
ENTER REMOVE, IDENTIFY, ONLY, OR (?):remove  
ENTER L# LIST OR (END):13  
DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS, CAPLUS'  
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n  
PROCESSING COMPLETED FOR L3  
L4                   2 DUPLICATE REMOVE L3 (3 DUPLICATES REMOVED)

=> d l4 1-2 bib ab

L4    ANSWER 1 OF 2           MEDLINE on STN                                   DUPLICATE 1  
AN    2005004008           MEDLINE  
DN    PubMed ID: 15611369  
TI    Functional variant of CYP4A11 20-hydroxyeicosatetraenoic acid  
synthase is  
      associated with essential hypertension.  
AU    Gainer James V; Bellamine Aouatef; Dawson Elliott P; Womble  
Kristie E;  
      Grant Sarah W; Wang Yarong; Cupples L Adrienne; Guo Chao-Yu;  
Demissie  
      Serkalem; O'Donnell Christopher J; Brown Nancy J; Waterman  
Michael R;  
      Capdevila Jorge H  
CS    Department of Medicine, Division of Clinical Pharmacology,  
Vanderbilt  
      University Medical School, Nashville, Tenn 37232-0146, USA.  
NC    CA68485 (NCI)  
      DK28350 (NIDDK)  
      DK38226 (NIDDK)  
      HL04221 (NHLBI)  
      HL60906 (NHLBI)  
      HL65193 (NHLBI)  
      HL67308 (NHLBI)  
      N01-HC-25195 (NHLBI)  
      RR00095 (NCRR)  
SO    Circulation, (2005 Jan 4) Vol. 111, No. 1, pp. 63-9.   Electronic  
Publication: 2004-12-20.  
      Journal code: 0147763. E-ISSN: 1524-4539.  
CY    United States  
DT    Journal; Article; (JOURNAL ARTICLE)  
LA    English  
FS    Abridged Index Medicus Journals; Priority Journals  
EM    200506  
ED    Entered STN: 20050105  
      Last Updated on STN: 20050628  
      Entered Medline: 20050627  
AB    BACKGROUND: The **CYP4A11 arachidonic acid**  
      monooxygenase oxidizes endogenous arachidonic acid (AA) to  
      20-hydroxyeicosatetraenoic acid (20-HETE), a metabolite with  
renovascular  
      and tubular functions. Mice with targeted disruption of  
Cyp4a14, a murine

homologue of CYP4A11, have severe hypertension. We combined molecular and

biochemical approaches to identify a functional variant of the CYP4A11 20-HETE synthase and determine its association with hypertensive status in 2 independent human populations.

#### METHODS AND

RESULTS: A thymidine-to-cytosine polymorphism at nucleotide 8590 resulted

in a phenylalanine-to-serine substitution at amino acid 434.

#### Expression

of cDNA with serine 434 resulted in a protein with a significantly reduced

AA and lauric acid metabolizing activity. In a population of 512 whites

from Tennessee, the age, body mass index, and gender-adjusted OR of having

hypertension attributable to the 8590C variant was 2.31 (95% CI 1.41 to

3.78) compared with the reference 8590TT genotype. In subjects from the

Framingham Heart Study, the adjusted ORs of hypertension associated with

the 8590C variant were 1.23 (CI 0.94 to 1.59; n=1538) in all subjects and

1.33 (CI 1.01 to 1.77; n=1331) when subjects with diabetes were excluded.

No association of the variant with hypertension was detected in a population of 120 blacks. CONCLUSIONS: We identified a variant of the

human CYP4A11 (T8590C) that encodes for a monooxygenase with reduced

20-HETE synthase activity. The association of the T8590C variant with

hypertension supports its role as a polygenic determinant of blood

pressure control in humans, and results obtained from the large population

database suggest that the relevance of the variant may vary according to

hypertension comorbidity.

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1998:394644 CAPLUS

DN 129:120516

TI Metabolism of arachidonic acid to 20-hydroxy-5,8,11,14-eicosatetraenoic

acid by P450 enzymes in human liver: involvement of CYP4F2 and CYP4A11

AU Powell, Pnina K.; Wolf, Imre; Jin, Rongyu; Lasker, Jerome M.

CS Department of Biochemistry, Mount Sinai School of Medicine, New York, NY,

USA

SO Journal of Pharmacology and Experimental Therapeutics (1998),  
285(3),

1327-1336

CODEN: JPETAB; ISSN: 0022-3565

PB Williams & Wilkins

DT Journal

LA English

AB 20-Hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) is a  
principal

arachidonic acid (AA) metabolite formed via P 450-dependent  
oxidation in

hepatic and renal microsomes. Although 20-HETE plays an  
important role in

the regulation of cell and/or organ physiol., the P 450 enzyme(s)  
catalyzing its formation in humans remain undefined. In this  
study, we

have characterized AA  $\omega$ -hydroxylation to 20-HETE by human  
hepatic

microsomes and identified the underlying P450s. Anal. of  
microsomal AA

$\omega$ -hydroxylation revealed biphasic kinetics ( $KM1$  and  $VMAX1 = 23$   
 $\mu M$

and  $5.5 \text{ min}^{-1}$ ;  $KM2$  and  $VMAX2 = 144 \mu M$  and  $18.8 \text{ min}^{-1}$ )  
consistent with

catalysis by at least two enzymes. Of the human P450s examined,  
CYP4A11 and

CYP4F2 were both potent AA  $\omega$ -hydroxylases, exhibiting rates of  
15.6

and  $6.8 \text{ nmol 20-HETE formed/min/nmol P 450, resp.}$  Kinetic  
parameters of

20-HETE formation by CYP4F2 ( $Km = 24 \mu M$ ;  $VMAX = 7.4 \text{ min}^{-1}$ ) and  
CYP4A11

( $KM = 228 \mu M$ ;  $VMAX = 49.1 \text{ min}^{-1}$ ) resembled the low and high  $KM$   
components, resp., found in liver microsomes. Antibodies to  
CYP4F2

markedly inhibited ( $93.4 \pm 6\%$ ;  $n = 5$ ) formation of 20-HETE by  
hepatic

microsomes, whereas antibodies to CYP4A11 were much less  
inhibitory

( $13.0 \pm 9\%$ ;  $n = 5$ ). Moreover, a strong correlation ( $r = 0.78$ ;  $P$   
 $< .02$ )

was found between microsomal CYP4F2 content and AA  
 $\omega$ -hydroxylation

among nine subjects. The correlation ( $r = 0.76$ ;  $P < .02$ ) also  
noted

between **CYP4A11** content and 20-**HETE** formation stemmed  
from the relationship ( $r = 0.83$ ;  $P < .02$ ) between hepatic CYP4A11  
and

CYP4F2 levels in the subjects. Finally, immunoblot anal.  
revealed that in

addition to liver, both P450s also were expressed in human  
kidney. Our

results indicate that AA  $\omega$ -hydroxylation in human liver is catalyzed

by two enzymes of the CYP4 gene family, namely CYP4F2 and CYP4A11, and

that CYP4F2 underlies most 20-HETE formation occurring at relevant AA

concns.

RE.CNT 54      THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s CYP4F (4A) HETE

L5              4 CYP4F (4A) HETE

=> s CYP4F (4A) (arachidonic acid)

L6              1 CYP4F (4A) (ARACHIDONIC ACID)

=> s l5 and l6

L7              1 L5 AND L6

=> d l7 bib ab

L7      ANSWER 1 OF 1    CAPLUS    COPYRIGHT 2006 ACS on STN

AN      2004:181462    CAPLUS

DN      140:402178

TI      Catalytic activity and isoform-specific inhibition of rat  
cytochrome P450

4F enzymes

AU      Xu, Fengyun; Falck, John R.; Ortiz de Montellano, Paul R.;  
Kroetz, Deanna

L.

CS      Department of Biopharmaceutical Sciences, University of  
California San

Francisco, San Francisco, CA, USA

SO      Journal of Pharmacology and Experimental Therapeutics (2004),  
308(3),

887-895

CODEN: JPETAB; ISSN: 0022-3565

PB      American Society for Pharmacology and Experimental Therapeutics

DT      Journal

LA      English

AB      Arachidonic acid is  $\omega$ -hydroxylated to 20-hydroxyeicosatetraenoic  
acid (20-HETE), which has effects on vasoactivity and renal  
tubular

transport and has been implicated in the regulation of blood  
pressure.

Cytochrome P 450 4A isoforms are generally considered the major  
arachidonic acid  $\omega$ -hydroxylases; however, little is known about

the

role of rat **CYP4F** isoforms in 20-**HETE** formation. The  
rat CYP4F isoforms, CYP4F1, CYP4F4, CYP4F5, and CYP4F6, were  
heterologously expressed in Escherichia coli, and their substrate

specificity in fatty acid metabolism was characterized. Substrate-binding assays indicated that leukotriene B<sub>4</sub> (LTB<sub>4</sub>) and arachidonic acid bound CYP4F1 and CYP4F4 in a type-I manner with a K<sub>s</sub> of 25 to 59 μM, and lauric acid bound CYP4F4 poorly. Reconstituted CYP4F1 and CYP4F4 catalyzed the ω-hydroxylation of LTB<sub>4</sub> with a K<sub>m</sub> of 24 and 31 μM, resp., and CYP4F5 had minor activity in LTB<sub>4</sub> metabolism. Importantly, CYP4F1 and CYP4F4 catalyzed the ω-hydroxylation of arachidonic acid with an apparent k<sub>cat</sub> of 9 and 11 min<sup>-1</sup>, resp. Lauric acid was a poor substrate for all of the CYP4F isoforms, and CYP4F6 had no detectable fatty acid ω-hydroxylase activity. The P 450 ω-hydroxylase inhibitors 17-octadecynoic acid, 10-undecynyl sulfate, and N-methylsulfonyl-12,12-dibromododec-11-enamide showed isoform-specific inhibition of CYP4F1- and CYP4F4-catalyzed ω-hydroxylation of arachidonic acid and potency differences between the CYP4A and CYP4F isoforms. These data support a significant role for CYP4F1 and CYP4F4 in the formation of 20-HETE and identify P 450 inhibitors that can be used to understand the relative contribution of the CYP4A and **CYP4F** isoforms to renal 20-**HETE** formation.

RE.CNT 40      THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT



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	ENTRY	SESSION
FULL ESTIMATED COST	19.21	19.42

=> s 17-ODECYNOIC ACID  
L3 0 17-ODECYNOIC ACID

=> s 17-OctaDECYNOIC ACID  
L4 670 17-OCTADECYNOIC ACID

=> s 14 (3A) structure  
L5 0 L4 (3A) STRUCTURE

=> s ((OctaDECYNOIC ACID) or (ODYA)) (3A) structure  
L6 1 ((OCTADECYNOIC ACID) OR (ODYA)) (3A) STRUCTURE

=> d 16 bib ab

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 1979:566794 CAPLUS  
DN 91:166794  
TI 4-Octadecyanoic acid, a largely regular  
structure in space group P.hivin.1  
AU Mo, Frode  
CS Inst. Roentgentek., Univ. Trondheim, Trondheim, Norway  
SO Acta Crystallographica, Section B: Structural Crystallography  
and Crystal  
Chemistry (1979), B35(9), 2135-40  
CODEN: ACBCAR; ISSN: 0567-7408  
DT Journal  
LA English

AB 4-Octadecynoic acid is triclinic, space group P.hivin.1, with a  
5.71(2)8,  
b 5.475(10), c 45.13(7) Å,  $\alpha$  92.55(15)°  $\beta$  93.15(15)° and  
 $\gamma$  123.95(25)°; Z = 4. The structure which has some OD  
character was solved in 2 discrete steps by direct and Patterson  
methods.  
Full-matrix least-squares refinement based on 1155 F0 from  
visually estimated  
film intensities was terminated at R = 0.071. In the ordered  
structure,  
neighboring carboxyl groups including the C atoms differ in  
relative  
orientation by .apprx.82°. Atoms of both triple-bond fragments  
are  
displaced from the plane of the main chain, probably largely  
because of  
the packing requirements of one of the carboxyl groups. The  
zigzag chains  
are tilted 20° away from the perpendicular to the Me end-group  
planes, and pack laterally according to a triclinic subcell.  
Mols. are  
linked together mainly as H-bonded dimers. The presence of  
stacking  
faults and possible disorder in one of the carboxyl groups  
suggests local  
alternative H-bond arrangements which would further stabilize  
the crystal  
structure.

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TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

19.21

19.42

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L3 0 17-ODECYNOIC ACID

=> s 17-OctaDECYNOIC ACID

L4 670 17-OCTADECYNOIC ACID

=> s l4 (3A) structure

L5 0 L4 (3A) STRUCTURE

=> s ((OctaDECYNOIC ACID) or (ODYA)) (3A) structure

L6 1 ((OCTADECYNOIC ACID) OR (ODYA)) (3A) STRUCTURE

=> d l6 bib ab

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN

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DN 91:166794

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AU Mo, Frode

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SO Acta Crystallographica, Section B: Structural Crystallography  
and Crystal

Chemistry (1979), B35(9), 2135-40

CODEN: ACBCAR; ISSN: 0567-7408

DT Journal

LA English

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b 5.475(10), c 45.13(7) Å,  $\alpha$  92.55(15)°  $\beta$  93.15(15)° and  
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orientation by .apprx.82°. Atoms of both triple-bond fragments  
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Mols. are  
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structure.